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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Patient-Reported Outcomes: Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis

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Background

Treatment with complement C5 inhibitors eculizumab (Ecu) and ravulizumab (Rav) inhibits terminal complement activity, improving hemoglobin (Hgb) levels and clinical outcomes for patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH), including reduced morbidity and mortality by preventing intravascular hemolysis (IVH), thrombotic events, hospitalizations, and death. In an analysis using data from the International PNH Registry (NCT01374360), Ecu improved pt survival through 20 y of real-world follow-up. Rav demonstrated a 98.4% survival rate up to 6 y in an open-label study (NCT03056040). Approximately 10-20% of pts experienced ongoing anemia caused by clinically significant extravascular hemolysis (cs-EVH). The phase 3, international, randomized, double-blind, placebo (Pbo)-controlled ALPHA (NCT04469465) superiority clinical trial assessed the effectiveness and safety of danicopan (Dan) add-on therapy to Rav or Ecu in pts with PNH and cs-EVH. This current analysis examined patient-reported outcomes (PROs) through wk 24.

Methods

Pts (≥18 y) with PNH and cs-EVH (Hgb ≤9.5 g/dL; absolute reticulocyte count ≥120×10^9/L) on Rav/Ecu >6 mo were randomized 2:1 to Dan or Pbo add-on therapy to Rav/Ecu for 12 wks (treatment period [TP] 1). At wk 12, Pbo arm pts switched to Dan (Pbo-Dan) and Dan arm pts continued treatment (Dan-Dan) for another 12 wks (TP2). The initial Dan dose of 150 mg TID could be escalated to 200 mg TID based on clinical response at investigator's discretion. Endpoints included change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score to wks 12 and 24 (key secondary) and changes in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 Scale (EORTC-QLQ-C30) global health status/QoL and physical functioning subscales and fatigue, nausea/vomiting, appetite loss, constipation, and diarrhea symptom subscales, and EuroQoL-5-Dimensions, 3-level version (EQ-5D-3L) to wk 24 (exploratory).

Results

As of 20 September 2022, 86 pts were randomized; 60 had completed (n=60) TP2 (Dan n=40; Pbo n=20). Baseline characteristics were similar between arms. The study met its primary endpoint of significant improvement in Hgb and all key secondary endpoints, including FACIT-Fatigue at wk 12 (data previously presented). Clinically meaningful (>5 point) and statistically significant increases from baseline in FACIT-Fatigue score were observed for Dan vs Pbo at wk 12 (least square mean difference [SEM] 7.97 [1.13] vs 1.85 [1.58]; *P*=0.0021). At wk 24 (**Fig 1**), outcomes were maintained in the Dan-Dan arm (40.32) and improved in Pbo-Dan arm (40.55) to levels similar to the general public score of 43.6. Significant improvements from baseline with Dan vs Pbo were demonstrated for EORTC-QLQ-C30 scores (physical function and social function within functional subscales, and fatigue within symptom subscales) at wk 12, maintained at wk 24 for the Dan-Dan arm, and demonstrated at wk 24 in Pbo-Dan arm (**Fig 2**). Trends in changes from baseline in other EORTC-QLQ-C30 function subscale scores paralleled that of the physical function subscale. EQ-5D-3L scores (US Health State Index) were similar between arms at baseline (Dan, 0.83; Pbo, 0.80), wk 12 (Dan, 0.90; Pbo, 0.86), and wk 24 (Dan-Dan, 0.90; Pbo-Dan, 0.87); scores at all timepoints are comparable to the general public (0.855-0.958). Dan demonstrated favorable benefit-risk profile with no deaths, meningococcal infections, or discontinuations due to hemolysis; additional safety analyses including adverse events were previously presented. No new safety signals were demonstrated.

Conclusions

These data suggest that Dan plus Rav or Ecu improves QoL compared to Rav or Ecu alone for pts with PNH and cs-EVH. In this phase 3, randomized, controlled superiority trial, improvements in clinically relevant PROs were observed in the Dan vs Pbo arm in the first double-blind 12 wks of treatment, and FACIT-Fatigue and EORTC-QLQ-C30 scores were maintained during the open-label period to wk 24 in the Dan-Dan arm and improved at wk 24 in Pbo-Dan arm to levels similar to those of the general public. Comparable EQ-5D-3L scores were maintained between arms across the study.

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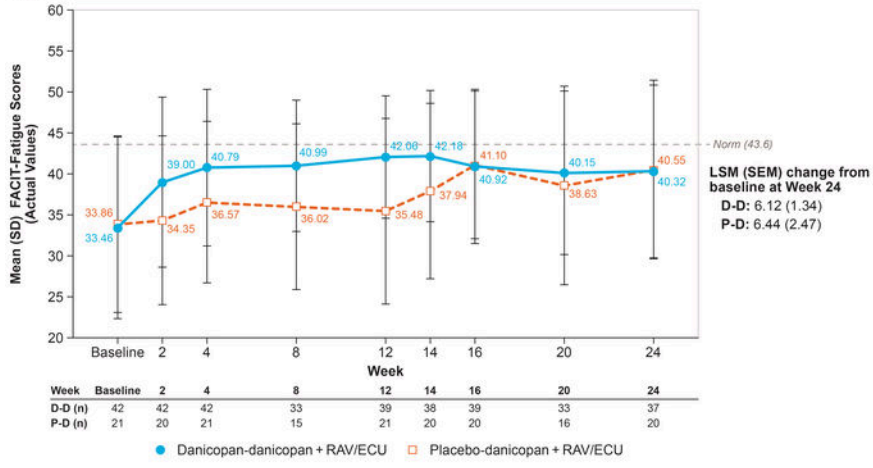
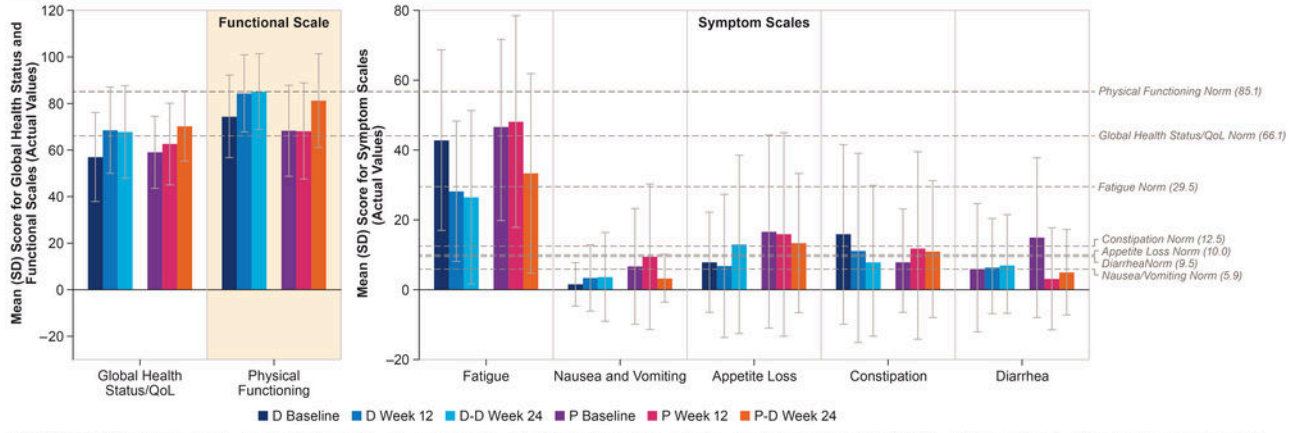
Figure 1.



Week	Baseline	2	4	8	12	14	16	20	24
D-D (n)	42	42	42	33	39	38	39	33	37
P-D (n)	21	20	21	15	21	20	20	16	20

FACIT-Fatigue score ranges from 0–52, with a higher score indicating less fatigue. Gray dotted line indicates the general norm population score. D (danicopan) or P (placebo) add-on therapy was received from baseline to wk 12. At week 12, P arm patients switched to D (P-D) and D arm patients continued D (D-D) for another 12 wks (wk 24). D-D, danicopan-danicopan; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale (version 4.0); LSM, least squares mean; P-D, placebo-danicopan.

Figure 2.



EORTC-QLQ-C30 includes a set of subscales that examine various aspects of quality of life, including fatigue. Each subscale has a range from 0–100%; a high score for a functional scale represents a high level of functioning, but a high score for a symptom scale represents more severe symptoms. Gray dotted line indicates the general population score. Trends in the other functional subscales (role, emotional, cognitive, and social functioning) not shown here were similar to the physical functioning subscale. There was little treatment effect on other symptom subscales not shown here (pain, dyspnea, insomnia, and financial difficulties). D (danicopan) or P (placebo) add-on therapy was received from baseline to wk 12. At week 12, P arm patients switched to D (P-D) and D arm patients continued D (D-D) for another 12 wks (wk 24). D-D, danicopan-danicopan; P-D, placebo-danicopan; QoL, quality of life.

Figure 1

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